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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/528,014	BARANY ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. The traversal is on the grounds(s) that it would not be undue burden to examine the claims of all groups I & II because the inventions are closely related and therefor would require common areas of search and consideration. However, it is maintained that undue burden would be required to examine the claims of group II along with claims of group I as evidenced by the fact that the claims of groups I and II have acquired a separate status in the art as recognized by their different classifications as recognized by their divergent subject matter and because a search of the subject matter of invention I is not co-extensive with a search of inventions II i.e. a search of invention II would require extensive search of probes and reagents not required for the search of invention I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-17 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are replete with redundant, superfluous and extraneous phrases as such, the claims are indefinite because they fail to distinctly claim the subject matter which applicant regards as his invention. It is suggested that the claims be amended to distinctly claim the subject matter.

a. Claims 1-17 are indefinite for the recitation "subjecting" because the term is a non-specific activity and therefore the method steps of subjecting are undefined. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter the claims encompass as well as make clear the subject matter from which others would be precluded. *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested that the claims be amended to recite positive and active method steps e.g. amplifying, digesting, ligating, hybridizing, destroying.

b. Claims 1-17 are indefinite in Claim 1, page 75, line 12 for the recitation "oligonucleotide primers are suitable for hybridization on complementary strands" because it is unclear whether the recitation is a method step of hybridization or a characteristic of the primers. It is suggested that Claim be amended to clarify e.g. replace "are suitable for hybridization" with "which hybridize".

c. Claims 1-17 are indefinite in Claim 1, page 75, line 12 for the recitation "complementary strands of a corresponding high and low abundance target nucleotide sequences" because "corresponding" is a non-specific relational term and therefore the relationship between the primers and target sequences is undefined. It is suggested that Claim 1 be amended to define the relationship e.g. delete "corresponding".

d. Claims 1-17 are indefinite in Claim 1, page 75, lines 21-27 for the recitation of polymerase chain reaction (PCR) cycle steps i.e. "comprising a denaturation.....primer is hybridized" because the steps are "conventional PCR procedures" (specification page 28, lines 14-15) and therefore repeated recitations of the steps throughout the claim is superfluous, redundant and confusing. It is suggested that Claim 1, page 75, lines 21-27; page 76, lines 13-16; and page 77, lines 8-12 be amended to clearly define the invention e.g. delete "comprising a denaturation.....primer is hybridized".

e. Claims 1-17 are indefinite in Claim 1, page 76, lines 1-2 for the recitation "oligonucleotide primers in a particular set are suitable for hybridization on complementary strands" because it is unclear whether the recitation is a method step of hybridization or a characteristic of the primers. It is suggested that Claim be amended to clarify e.g. replace "are suitable for hybridization on" with "which hybridize to". The recitation is further indefinite because it is unclear whether the "secondary primers in a particular set" refer to a "particular set" which differs from the "secondary primer set". It is suggested that Claim 1 be amended to specifically define the primer sets.

f. Claims 1-17 are indefinite in Claim 1, page 77, lines 2-3 for the recitation "primers may be used to amplify all of the secondary extension products" because it is unclear whether the recitation is a method step or a characteristic of the primers. It is suggested that the claim be amended to clarify e.g. replace "may be used to amplify all of" with "are amplification primers for amplification of all".

g. Claims 1-17 are indefinite in Claim 1, page 77, line 18 for the recitation "probes in a particular set are suitable for ligation" because it is unclear whether the recitation is a method step or a characteristic of the probe. It is suggested that the claim be amended to clarify e.g. replace "are suitable for ligation" with "ligate".

h. Claims 1-17 are indefinite in Claim 1, page 77, line 21 for the recitation "such ligation" because it is whether the previous ligation reaction is being referenced. It is suggested that the claims be amended to clarify e.g. replace "such" with "said".

i. Claims 1-17 are indefinite in Claim 1, page 78, line 6 for the recitation "thereby indicating the presence of one or more low abundance target nucleotide...." because "indicating" is non-specific relational term and therefore the relationship between the labels and targets is undefined. It is suggested that Claim 1, page 78, line 6 be amended to define the relationship i.e. replace "indicating" with "identifying".

j. Claim 2 is indefinite in the recitation "particular probe set" because it is unclear what "probe set" is being described. It is suggested that the claim be amended to clarify e.g. delete "particular".

k. Claim 2 is indefinite in the recitation "a unique length so that the ligation" because "so that" is a non-specific relational term and therefore the relationship between the probe length and ligation is undefined. It is suggested that the claim be amended to clarify e.g. replace "so that" with "whereby".

l. Claim 2 is indefinite in the recitation "ligation product sequences which they form can be distinguished" because it is unclear whether the sequences are distinguished. It is suggested that the claim be amended to clarify e.g. replace "can be" with "are".

m. Claim 2 is indefinite in the recitation "other nucleic acids" because the recitation lacks proper antecedent basis in the claim which recites 'ligation product sequences". It is suggested that the claim be amended to provide proper antecedent basis e.g. replace "nucleic acids" with "ligation product sequences".

n. Claim 3 is indefinite in lines 18-19 for the recitation "wherein the second oligonucleotide probe of each oligonucleotide probe set has an addressable..." because it is unclear whether the recitation is further limitation of the probe. It is suggested that the claim be amended to clarify e.g. replace "has" with "further comprises".

o. Claim 3 is indefinite in lines 21-22 for the recitation "different capture oligonucleotides immobilized at different particular sites" because it is unclear how the oligonucleotides differ from each other, how the sites differ from each other and how the different oligonucleotides and difference sites relate to each other. It is suggested that the claim be amended to clarify e.g. "a solid support comprising an array address-specific capture oligonucleotides" (specification, page 36, lines 22-30).

p. Claim 3 is indefinite in the recitation "under conditions effective to hybridize the ligation product" because it is unclear whether the recitation is a method step of hybridization. It is suggested that the claim be amended to clarity e.g. delete "under conditions effective".

q. Claim 3 is indefinite in lines 30 and 34 for the recitations "indicates the presence" and "indicating the presence" because "indicating" is non-specific relational term and therefore the relationship between the "detection" and "ligation product sequences" is undefined. It is suggested that the claim be amended to clarify e.g. replace "indicates" and "indicating" with "identifies" and "identifying".

r. Claims 4-7 are indefinite in Claim 4, lines 2-6 for the recitation "differing by one or more.....plurality of target nucleotides" because the recitation is redundant and therefore confusing. It is suggested that Claim 4 be amended to clearly recite the invention e.g. delete the redundant recitation.

s. Claims 4-7 are indefinite in lines 1-2 for the recitation "wherein the relative amounts" because "relative" is a comparative term with requires definition or criteria for determining. It is suggested that Claim 4 be amended to define "relative" or recite criteria for determining "relative".

t. Claims 4-7 are indefinite in Claim 4, lines 7-9 and 17 because the recitations are method steps for "quantifying" but the steps are missing the elements of quantification. It is suggested that Claim 4 be amended to recite positive and active method steps for quantifying e.g. "quantifying the amounts of primary extension products by comparing said primary extension products to an internal standard" (specification, page 41, lines 8-12).

u. Claims 4-7 are indefinite in Claim 4, lines 7-9 for the recitation "after said subjecting the primary polymerase chain reaction mixture to one or more polymerase chain reaction cycles" because the primary extension products are present and quantifiable only after the primary PCR step (Claim 1, page 75, lines 20-27) and therefore the recitation is redundant and confusing. It is suggested that Claim 4 be amended to clarify e.g. delete "after said subjecting

the primary polymerase chain reaction mixture to one or more polymerase chain reaction cycles" and add after "products" the recitation "before the secondary polymerase chain reaction".

v. Claims 4-7 at indefinite in Claim 4, line 21 for the recitation "to provide a quantitative measure of the relative level of one or more" because "relative level" is a non-sequitur to "quantitative measure" and because "relative" is a comparative term but it is unclear to what the sequences are being compared. It is suggested that Claim 4 be amended to clarify e.g. delete "of the relative level".

w. Claims 5-7 and 11-14 are indefinite in each claim for the recitation "relative amounts" because is a comparative term with requires definition or criteria for determining. It is suggested that the claims be amended to define "relative" or recite criteria for determining "relative".

x. Claims 5-7 and 11-14 are indefinite in each claim for the recitation "differing by one or more....unknown amounts" because the recitation is redundant and therefore confusing. It is suggested that the claim be amended to clearly recite the claimed invention i.e. delete "differing by one or more....unknown amounts".

y. Claims 8-11 are indefinite in Claim 8 for the recitation "the efficiency and accuracy of converting" because the recitation lacks proper antecedent basis in the Claim 1. It is suggested that Claim 8 be amended to provide proper antecedent basis e.g. delete "wherein the efficiency.....is improved by" and to recite "further comprising performing the following step prior to providing the secondary oligonucleotide primer set to thereby improve the efficiency and accuracy of producing a secondary PCR product containing a restriction endonuclease site":.

z. Claim 8-11 are indefinite in Claim 8, line 20 for the recitation "a particular set are suitable for hybridization on" because it is unclear whether the recitation is a method step of

hybridization. It is suggested that Claim 8 be amended to clarify e.g. replace "are suitable for hybridization on" with "hybridize to".

aa. Claims 8-11 are indefinite in Claim 8, line 20 for the recitation "a particular set" because "particular" it is unclear which "set" is being described. It is suggested that the claim be amended to clarify.

bb. Claim 8-11 are indefinite in Claim 8, lines 21-22 for the recitation "primary extension product to permit formation of a pre-secondary polymerase chain reaction product" because it is unclear whether the pre-secondary product is formed. It is suggested that Claim 8 be amended to clarify e.g. replace "permit formation of" with "form".

cc. Claim 9 is indefinite in the recitation "particular probe set" because it is unclear what "probe set" is being described. It is suggested that the claim be amended to clarify e.g. delete "particular".

dd. Claim 9 is indefinite in the recitation "a unique length so that the ligation" because "so that" is a non-specific relational term and therefore the relationship between the probe length and ligation is undefined. It is suggested that the claim be amended to clarify e.g. replace "so that" with "whereby".

ee. Claim 9 is indefinite in the recitation "ligation product sequences which they form can be distinguished" because it is unclear whether the sequences are distinguished. It is suggested that the claim be amended to clarify e.g. replace "can be" with "are".

ff. Claim 9 is indefinite in the recitation "other nucleic acids" because the recitation lacks proper antecedent basis in the claim which recites 'ligation product sequences". It is suggested that the claim be amended to provide proper antecedent basis e.g. replace "nucleic acids" with "ligation product sequences".

gg. Claim 10 is indefinite in lines 22-23 for the recitation "wherein the second oligonucleotide probe of each oligonucleotide probe set has an addressable" because it is

unclear whether the recitation is further limitation of the probe. It is suggested that the claim be amended to clarify e.g. replace "has" with "further comprises".

hh. Claim 10 is indefinite in lines 25-26 for the recitation "different capture oligonucleotides immobilized at different particular sites" because it is unclear how the oligonucleotides differ from each other, how the sites differ from each other and how the different oligonucleotides and difference sites relate to each other. It is suggested that the claim be amended to clarify e.g. "a solid support comprising an array address-specific capture oligonucleotides" (specification, page 36, lines 22-30).

ii. Claim 10 is indefinite in the recitation "under conditions effective to hybridize the ligation product" because it is unclear whether the recitation is a method step of hybridization. It is suggested that the claim be amended to clarity e.g. delete "under conditions effective".

jj. Claim 10 is indefinite in the recitations "indicates the presence" and "indicating the presence" because "indicating" is non-specific and a non sequitur to the "method for identifying". It is suggested that the claim be amended to replace "indicates" and "indicating" with "identifies" and "identifying".

kk. Claim 17 is indefinite on page 83, lines 27-30 for the recitation "repeating the endonuclease digestion reaction.....one or more ligase detection reaction cycles" because it is unclear whether the repeated reaction comprises secondary extension products. It is suggested that the claim be amended to clarify e.g. replaces lines 27-30 with "further comprising: blending the ligation product sequences and the restriction endonuclease wherein the restriction endonuclease recognizes and cleaves.....".

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3-7 & 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (WO 97/31256, published 28 August 1997) in view of Jacobson et al. (Oncogene, 1994, 9: 553-563).

Regarding Claim 1, Barany et al. teach a method for identifying one or more sequences differing by one or more single-base changes, insertions or deletion in a plurality of target nucleotide sequences in a sample (page 10, lines 23-26) comprising: blending the sample, primary oligonucleotide primers and polymerase and performing a polymerase chain reaction (PCR) to produce primary extension products; providing a plurality of probe sets wherein a first probe, having an extension-specific portion and a detectable label and a second probe having an extension-specific portion wherein the probe of a set ligate together when hybridized adjacent to one another on a complementary extension product-specific portion; and detecting the labels of the ligation products to thereby identify the presence of one or more target sequences in the sample (page 15, line 16-page 16, line 29). Barany et al. do not teach the method wherein after the PCR, a second PCR is performed to produce secondary PCR products comprising a restriction enzyme site followed by restriction enzyme digestion and a third PCR. Jacobson et al. teach a similar method comprising: blending the sample, primary oligonucleotide primers and polymerase and performing PCR to produce primary extension products; blending the primary extension products, secondary primers to produce secondary extension products; subjecting the secondary extension products to an endonuclease digestion reaction thus destroying the high abundance secondary extension products; and performing a third PCR (page 554, Fig. 1) wherein the secondary primers have target-specific portions and produce secondary PCR products comprising a restriction enzyme site (page 554, Fig. 1, step 2) wherein the method identifies one or more low abundance sequences differing by one or more

single-base changes (K-ras mutant) from a high abundance sequence (wild type) in a plurality of target sequences (page 555, left column, second full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single PCR amplification of Barany et al. by adding a secondary PCR to incorporate a restriction enzyme site into the PCR products as taught by Jacobson et al. for the expected benefit of producing a higher quantity of sequence-specific sequences and to thereby detect and identify a low abundance sequence of interest within a sample containing high abundance sequences as taught by Jacobson et al. (page 555, left column, second full paragraph).

Regarding Claim 3, Barany et al. teach the method wherein a probe of each probe set has an addressable array-specific portion said method further comprising: providing a solid support with different capture oligonucleotides immobilized at different sites wherein the capture oligonucleotides have sequences complementary to the addressable array-specific portions; and contacting the ligation products with the solid support to capture the addressable array-specific portions to the solid support; and detecting the presence of ligation product immobilized to the solid support (page 11, lines 1-16).

Regarding Claim 4, Barany et al. teach the method wherein the relative amounts of the one or more sequences is quantified by comparing the amount of ligation product sequences generated to ligation products generated from known amounts of marker sequences (page 19, lines (page 19, lines 16-34).

Regarding Claim 5, Barany et al. teach as few as a single molecule can be detected (page 22, lines 33-37) but they do not teach the molar ratio of low to high abundance sequences. However, Jacobson et al. teach the similar method wherein the relative amounts of low abundance to high abundance ratio is less than 1:1,000 (page 555, left column second full paragraph, lines 8-10).

Regarding Claim 6, Barany et al. teach as few as a single molecule can be detected (page 22, lines 33-37) but they do not teach the molar ratio of low to high abundance

sequences. However, Jacobson et al. teach the similar method wherein the relative amounts of low abundance to high abundance ratio is less than 1:10,000 (page 555, left column second full paragraph, lines 8-10).

Regarding Claim 7, Barany et al. teach as few as a single molecule can be detected (page 22, lines 33-37) but they do not teach the molar ratio of low to high abundance sequences. However, Jacobson et al. teach the similar method wherein the relative amounts of low abundance to high abundance ratio is less than 1:100,000 (page 555, left column second full paragraph, lines 8-10).

Regarding Claim 17, Barany et al. do not teach including the a restriction enzyme digestion step. However, Jacobson et al. teach the similar method wherein the restriction enzyme digestion is repeated to selectively destroy the high abundance extension products. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have included the restriction enzyme digestion taught by Jacobson et al. and to repeat the digestion to thereby enrich for the sequence of interest and detect a low abundance sequence within a sample comprising high abundance sequences as taught by Jacobson et al. (page 555, left column, second full paragraph).

6. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (WO 97/31256, published 28 August 1997) in view of Jacobson et al. (Oncogene, 1994, 9: 553-563) as applied to claims 1, 3-7 and 17 above and further in view of Day et al. (Genomics, 1995, 29: 152-162).

Regarding Claim 2, Barany et al. teach the method for identifying one or more sequences differing by one or more single-base changes, insertions or deletion in a plurality of target nucleotide sequences in a sample (page 10, lines 23-26) wherein the probes in a particular set have are designed so that the ligation product sequences which they form are

distinguished from other sequences: wherein the ligation products are separated and distinguished (page 14, lines 26-38) but they do not teach the ligation products are separated and distinguished by electrophoretic mobility. However, Day et al. teach a similar method comprising: blending the sample, primary oligonucleotide primers and polymerase and performing a polymerase chain reaction (PCR) to produce primary extension products; providing a plurality of probe sets wherein a first probe, having an extension-specific portion and a detectable label and a second probe having an extension-specific portion wherein the probe of a set ligate together when hybridized adjacent to one another on a complementary extension product-specific portion; and detecting the labels of the ligation products to thereby identify the presence of one or more target sequences in the sample wherein the primers in a particular probe set have a unique length (page 157, Fig. 2) whereby ligation products are separating and distinguishing by electrophoretic mobility (page 154, left column, third full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Barnay so as to detect the ligation product using the electrophoretic mobility assay taught by Day et al. for the expected benefits of speed, sensitivity and accuracy i.e. identifying ligation products within a single multiplex reaction by using an automated sequencer and sequencing software as taught by Day et al. (page 161, left column last paragraph).

7. Claims 8 and 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (WO 97/31256, published 28 August 1997) in view of Jacobson et al. (Oncogene, 1994, 9: 553-563) as applied to claims 1, 3-7 and 17 above and further in view of Cook et al. (U.S. Patent No. 5,859,221, filed 6 June 1995).

Regarding Claim 8, Barany et al. teach the method for identifying one or more sequences differing by one or more single-base changes, insertions or deletion in a plurality of target nucleotide sequences in a sample (page 10, lines 23-26) wherein the primers comprise

nucleotide analogs (page 13, lines 35-38) but they do not teach the method comprising a pre-secondary oligonucleotide primer set wherein at least one primer contains one or more nucleotide analogs. However, multiple PCR amplifications nucleotide analogs were well known in the art at the time the claimed invention was made. Specifically, Cook et al. teach thatsequences comprising nucleotide analogs resist nuclease degradation and hybridize with greater fidelity (Column 4, lines 38-42). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primer of Barany et al. to comprise one or more nucleotide analogs for the expected benefits of resistance to nuclease degradation and greater fidelity of hybridization as taught by Cook et al. (Column 4, lines 38-42). The skilled practitioner in the art would have been further motivated to modify the PCR amplifications of Barany et al. and Jacobson et al. to perform a pre-secondary amplification for the known benefits of PCR i.e. sensitivity and increased product yield as taught by Barany et al. (page 7, lines 32-35).

Regarding Claim 10, Barany et al. teach the method wherein a probe of each probe set has an addressable array-specific portion said method further comprising: providing a solid support with different capture oligonucleotides immobilized at different sites wherein the capture oligonucleotides have sequences complementary to the addressable array-specific portions; and contacting the ligation products with the solid support to capture the addressable array-specific portions to the solid support; and detecting the presence of ligation product immobilized to the solid support (page 11, lines 1-16).

Regarding Claim 11, Barany et al. teach the method wherein the relative amounts of the one or more sequences is quantified by comparing the amount of ligation product sequences generated to ligation products generated from known amounts of marker sequences (page 19, lines (page 19, lines 16-34).

Regarding Claim 12, Barany et al. teach as few as a single molecule can be detected (page 22, lines 33-37) but they do not teach the molar ratio of low to high abundance

sequences. However, Jacobson et al. teach the similar method wherein the relative amounts of low abundance to high abundance ratio is less than 1:1,000 (page 555, left column second full paragraph, lines 8-10).

Regarding Claim 13, Barany et al. teach as few as a single molecule can be detected (page 22, lines 33-37) but they do not teach the molar ratio of low to high abundance sequences. However, Jacobson et al. teach the similar method wherein the relative amounts of low abundance to high abundance ratio is less than 1:10,000 (page 555, left column second full paragraph, lines 8-10).

Regarding Claim 14, Barany et al. teach as few as a single molecule can be detected (page 22, lines 33-37) but they do not teach the molar ratio of low to high abundance sequences. However, Jacobson et al. teach the similar method wherein the relative amounts of low abundance to high abundance ratio is less than 1:100,000 (page 555, left column second full paragraph, lines 8-10).

Regarding Claim 15, Barany et al. and Cook et al. do not teach the analog of at least one primer is at the 3' end of the primer. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Cook et al. wherein the analogs resist nuclease digestion and hybridize with greater fidelity to the primers of Barany et al. and Jacobson et al. and to place an analog at the 3' end of at least on primer for the expected benefit of preventing digestion from nuclease which are known in the art to digest nucleic acid sequences from the 3' end and for the expected benefit of increasing 3' end hybridization fidelity to thereby improve PCR primer extension which is known in the art to depend upon the 3' primer-template hybridization.

Regarding Claim 16, Barany et al. do not teach the claimed nucleotide analogs. However, Cook et al. teach the claimed analogs (Column 6, lines 8-29). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primer of Barany et al. to comprise one or more nucleotide analogs for the expected benefits

of resistance to nuclease degradation and greater fidelity of hybridization as taught by Cook et al. (Column 4, lines 38-42).

8. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (WO 97/31256, published 28 August 1997) in view of Jacobson et al. (Oncogene, 1994, 9: 553-563) and Cook et al. (U.S. Patent No. 5,859,221, filed 6 June 1995) as applied to claims 8 and 10-16 above and further in view of Day et al. (Genomics, 1995, 29: 152-162).

Regarding Claim 9, Barany et al. teach the method for identifying one or more sequences differing by one or more single-base changes, insertions or deletion in a plurality of target nucleotide sequences in a sample (page 10, lines 23-26) wherein the ligation products are separated and distinguished (page 14, lines 26-38) but they do not teach the ligation products are separated and distinguished by electrophoretic mobility. However, Day et al. teach a similar method comprising: blending the sample, primary oligonucleotide primers and polymerase and performing a polymerase chain reaction (PCR) to produce primary extension products; providing a plurality of probe sets wherein a first probe, having an extension-specific portion and a detectable label and a second probe having an extension-specific portion wherein the probe of a set ligate together when hybridized adjacent to one another on a complementary extension product-specific portion; and detecting the labels of the ligation products to thereby identify the presence of one or more target sequences in the sample wherein the primers in a particular probe set have a unique length (page 157, Fig. 2) whereby ligation products are separating and distinguishing by electrophoretic mobility (page 154, left column, third full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the ligation product identification of Barany et al. with the electrophoretic mobility identification taught by Day et al. for the expected benefits of with speed, sensitivity and accuracy i.e. identifying ligation products within a single multiplex

reaction by using an automated sequencer and sequencing software as taught by Day et al. (page 161, left column last paragraph).

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
May 10, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600
5/14/01